

## Accepted Manuscript

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PII: S0927-7765(16)30221-1  
DOI: <http://dx.doi.org/doi:10.1016/j.colsurfb.2016.03.066>  
Reference: COLSUB 7773

To appear in: *Colloids and Surfaces B: Biointerfaces*

Received date: 16-12-2015  
Revised date: 15-3-2016  
Accepted date: 22-3-2016

Please cite this article as: Kofi Asare-Addo, Enes Supuk, Mohammed H. Mahdi, Adeola O. Adebisi, Elijah Nep, Barbara R. Conway, Waseem Kaialy, Hiba Al-Hamidi, Ali Nokhodchi, Drug release from E chemistry hypromellose tablets using the Bio-Dis USP type III apparatus: An evaluation of the effect of systematic agitation and ionic strength, *Colloids and Surfaces B: Biointerfaces* <http://dx.doi.org/10.1016/j.colsurfb.2016.03.066>

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# Drug release from E chemistry hypromellose tablets using the Bio-Dis USP type III apparatus: An evaluation of the effect of systematic agitation and ionic strength

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## Statistical Summary

Total number of words including title page and references: 7109

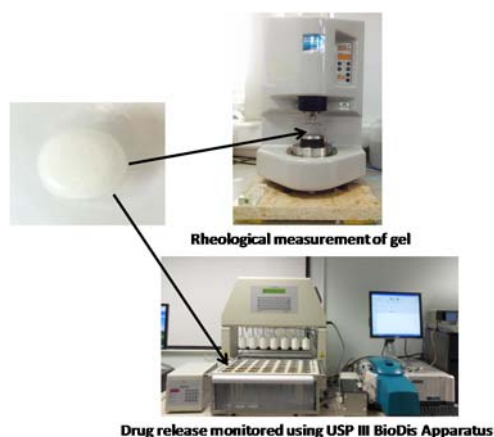
Total number of pages without title page and references: 5275

Total number of tables: 3

Total number of figures: 5

Total number of supplementary figures: 7

## Graphical Abstract



## Highlights

- E50LV, E4M and E10M HPMC polymers are effective in dissipating electrostatic charge of the API (theophylline)
- Triboelectrification enabled optimum charge to mass ratio to be measured.
- Systematic agitation has effect on drug release from E50LV and E4M
- Stiffness of gel increases with increasing molecular weight
- E10M tablet matrices most resilient of matrices tested

## Abstract

The aim of the study was to evaluate the effect of systematic agitation, increasing ionic strength and gel strength on drug release from a gel-forming matrix (HPMC E10M, E4M and E50LV) using USP type III Bio-Dis apparatus with theophylline as a model drug. The triboelectric charging; particle sizing, water content, true density and SEM of all the hypromellose grades, theophylline and formulated blends were characterised. The results showed that balanced inter-particulate forces exist between drug particles and the excipient

surface and this enabled optimum charge to mass ratio to be measured. Agitation and ionic strength affected drug release from E50LV and E4M tablet matrices in comparison to the E10M tablet matrices. Drug release increased substantially when water was used as the dissolution media relative to media at pH 1.2 (containing 0.4 M NaCl). The results showed all  $f_2$  values for the E10M tablet matrices were above 50 suggesting the drug release from these tablet matrices to be similar. Rheological data also explained the different drug release behaviour with the stress required to yield/erode being 1 Pa, 150 Pa, and 320 Pa, for the E50LV, E4M and E10M respectively. The stiffness of the gel was also found to be varied from 2.5 Pa, 176.2 Pa and 408.3 Pa for the E50 LV, E4M and E10M respectively. The lower  $G'$  value can be explained by a softer gel being formed after tablet introduction into the dissolution media thereby indicating faster drug release.

Keywords: Agitation sequence; ionic concentration strength; HPMC polymeric matrix tablets triboelectrification, USP III apparatus, rheology

## 1. Introduction

Polymer based matrix systems are popular in controlled release formulations in terms of economic, process development and scale up procedures [1-5]. Polymer-based matrix tablets swell once in contact with fluid, forming a gel-layer, which controls drug release from the formulation. The release of drug from the swollen gel matrix depends on the possible interactions between the aqueous dissolution medium, polymer, drug and other tablet ingredients [6-8]. An important factor that affects bioavailability of drugs is the presence of food due to potential interactions that may occur between the formulation and the food [9, 10] such as chelation of penicillamine by iron in the gut leading to reduction in its absorption and activity. Furthermore, the physiological response to ingestion of food such as gastric acid secretion may increase or decrease the bioavailability of some drugs [11-13]. pH and ionic strength of the gastrointestinal (GI) fluids vary greatly along the GI tract under both fasted and fed conditions [14, 15] and this can affect the rate at which a drug is released from hydrophilic extended release (ER) matrices [16-20]. The gel layer formed around hydrophilic matrices, upon its contact with GI fluids, is eroded allowing drug release. Erosion is the dominant release mechanism for poorly soluble drugs, whereas the soluble portion of drug is released by diffusion through the gel layer [9, 10, 21-23]. Due to the non-ionic nature of hydroxypropyl methylcellulose (HPMC), when drug solubility is pH- independent, the matrices also exhibit pH-independent drug releases profiles [24]. The high molecular weight

chemistries are the most widely used polymers in ER matrix formulations, e.g., METHOCEL™ Premium K (hypromellose 2208, USP) and E (hypromellose 2910, USP). The HPMC substitution type and molecular weight has an effect on the amount of water bound to the polymer [25]. According to Aoki and co-workers [26], during the initial stage of dissolution, water penetrates into the matrix and usually acts as non-freezing (bound) water. In the next stage, the water content of the matrix increases and freezable water is detected at levels that are related to drug release. They also reported that the transport of solutes mainly occurs through the free water and that only little transport occurs through bound water. Yoshioka and coworkers [27], studied hydrophilic polymeric gelatin gels and claimed that bound water did not participate to any significant effect in the hydration process and that the hydrolysis/water-uptake rate depended mainly on the amount of free water present in the system. Therefore, determining the dynamics and state of water molecules in hydrogels enables a better understanding of the swelling process of the hydrophilic matrices and the release of drugs from these systems [28]. Three types of hydration water has been reported [29] with each possessing different physical properties; Type I (freezing or free, bulk-like water) melts at the normal melting point of pure water (0 °C); Type II (freezing or bound water) interacts weakly with macromolecules and displays a lower melting point than pure water (< 0 °C) and Type III (bound water) which interacts strongly with hydrophilic and ionic groups of the polymer and shows non-freezing behaviour.

Pharmaceutical powders are prone to electrostatic charging because they normally have a high electrical resistance, preventing charge dissipation. Triboelectrification is a phenomenon which refers to electrostatic charge being generated due to the difference in electrical potential when two materials come into contact with each other. The ability to control the charging of pharmaceutical powders is essential in improving the quality of the end product and minimising powder loss. Triboelectrification is used to help with the mixing operations in industry [30, 31] More recently, the triboelectric charging behaviour of E4M, K4M and their powder blends with theophylline, were studied. It was shown that when theophylline was mixed with hypromellose grades of opposite polarities, the triboelectric charge of the final powder mixture was decreased forming a stable ordered mixture believed to result in a more homogenous and stable system [32].

In the present work, three grades of the E chemistry HPMC polymer, and their formulated blends were characterised by triboelectrification, particle sizing and particle morphology. Theophylline release from these polymers were assessed with varying agitation sequences, ionic strengths and pH levels using the USP III apparatus to discriminate between the

performances of the polymers. This study was performed with a view to differentiate between poor and robust sustained release formulations. Rheological experiments were also conducted to ascertain the influence of the various ionic strengths on the gel layer produced from these polymers.

## 2. Materials and methods

### 2.1. Materials

HPMC E chemistry grades METHOCEL™, E50LV, E4M and E10M supplied by Colorcon UK were used as the hydrophilic matrix formers. Anhydrous theophylline was obtained from Sigma, UK. Dissolution buffers were prepared according to the USP 2003 [33] using the following materials: potassium chloride (Acros Organics, UK) and hydrochloric acid (Fisher Scientific, UK) for dissolution media at pH 1.2 and pH 2.2; potassium phosphate monobasic (Fisher BioReagents, UK) and sodium hydroxide (Fisher Scientific, UK) for dissolution media at pH 5.8, 6.8, 7.2 and 7.5 .

### 2.2. Powder characterisation

#### *2.2.1. Electrostatic properties of pure polymers and formulated blends*

A triboelectric device based on a shaking concept, previously described by Šupuk and co-workers [34-36] was used to investigate the triboelectrification of theophylline, the three HPMC E chemistry polymers and their formulation blends (the formulation blends were in the ratio of 4:1 (drug: HPMC) for 10 min at 100 rpm in a Turbula® mixer. This is further detailed in section 2.6) by determining the charge-to-mass ratio. In this work, the charge-to-mass ratio of the bulk powders was measured after shaking using a custom-made Faraday cup connected to an electrometer (Keithley Model 6514). If a positively-charged particle enters the Faraday cup, a negative charge is induced and distributed on the inner surface of the Faraday cup, whilst a positive charge is distributed over the outer surface of the cup, setting up an electric field and a potential difference between the two cups. The capacitance  $C$  between the inner and outer cups acquires a potential,  $V = q/C$  which is measured by an electrometer connected to an inner cup. The charge-to-mass ratio is obtained by dividing the net charge measured and the mass of the sample tested. Tests were carried out under ambient temperature (22 °C) and humidity (35 - 47 %RH).

## 2.3. Micromeritic properties of polymers

### 2.3.1. Particle size analysis

Particle size distribution (PSD) analysis was conducted on an aerosolised dry samples of the HPMC E50LV, E4M and E10M using a Sympatec (Clausthal-Zellerfeld, Germany) laser diffraction particle size analyser as described previously [37].

### 2.3.2. True density measurements

The Ultrapycnometer 100 (Quantachrome Instruments) was used in the determination of the true density of powder mixtures used for the tableting. The test was carried out using a multi-run system with a standard deviation of 0.005 %. The results presented are the mean and standard deviation of a minimum of three determinations.

### 2.3.3. Surface area measurements

Brunauer–Emmett–Teller (BET) surface area was measured by nitrogen adsorption using Micromeritics Gemini 6 (Norcross, USA) automated gas sorption system model. The determination of external surface area was estimated by using the standard t-plot calculations by using experimental points at a relative pressure of  $P/P_0 = 0.1 - 0.5$ . All measurements were done in triplicate. Surface roughness of different polymers tested was calculated based on the ratio between BET surface area and theoretical surface area [37]

### 2.3.4. Water content analysis

The moisture content of the samples was determined semi-automatically by the Karl Fisher method (Mettler Toledo, C20 Coulometric KF Titrator, Switzerland). The Fischer reagent solution was Hydranal<sup>®</sup> Coulomat AF (Sigma Aldrich, USA).

## 2.4. Scanning electron microscopy (SEM)

Electron micrographs of all polymers were obtained using a scanning electron microscope (SEM) (Philips XL 20, Eindhoven, Netherlands) operating at either 2 or 5 kV. The samples were mounted on a metal stub with double-sided adhesive tape and coated under vacuum with gold in an argon atmosphere prior to observation. Several magnifications (x100 -3000 magnifications) were used to observe the shape and surface topography of particles of the different HPMC grades.

## 2.5. Rheological measurements

### 2.5.1 *Sample preparation of rheological study*

Two sets of samples were prepared from E50V, E4M and E10M HPMC polymers to make 5 % w/v into pH 1.2 media (no NaCl) and pH 1.2 media (0.4M NaCl) at  $37 \pm 0.5$  °C. The samples were then subjected to rheological measurements to investigate their stiffness and the strength of the gel after the swelling process in the media. All rheological measurements were performed using a Bohlin Gemini Nano HR rheometer (Malvern Instruments, Worcestershire, UK) fitted with 55 mm parallel-plate geometry.

### 2.5.2. *Yield stress determination*

Stress sweep rheological studies were used to determine yield stress of different gel formulations to predict the stress required to initiate erosion. The stress was gradually increased from 0.1 Pa to 1000 Pa at  $1.5 \text{ rad s}^{-1}$  angular frequency. All measurements were taken at  $37 \pm 0.5$  °C.

### 2.5.3. *Frequency Sweep measurement*

The rheological behaviour of the samples was evaluated in terms of the elastic (storage) modulus ( $G'$ ) and the viscous (loss) modulus ( $G''$ ) as a function of angular frequency (0.1–100  $\text{rad s}^{-1}$  angular frequency) to produce mechanical spectra of the samples. Measurements were taken at  $37 \pm 0.5$  °C and performed at 0.5 % strain (strain amplitude chosen was within the linear viscoelastic region of the sample).

### 2.5.4. *Single frequency measurement*

Oscillation mode (single frequency –stress control) was used to determine the viscoelasticity of the gel formed after swelling. In order to understand how the elastic modulus ( $G'$ ) of the gel was affected by the different HPMC grades, a 5 %w/v of each of the E chemistry HPMC grades was dispersed in media at pH 1.2 at  $37 \pm 0.5$  °C and left to hydrate for 1 h before rheological measurements were obtained.

The measurements were recorded at  $1.5 \text{ rad s}^{-1}$  angular frequency and 0.5 % strain with a 0.6 mm gap. The strain amplitude chosen was within the linear viscoelastic region of the samples. All measurements were taken at  $37 \pm 0.5$  °C.



## 2.6. Tablet preparation and mechanical strength test

Round cylindrical tablets with a diameter of  $9.6 \pm 0.1$  mm and the target weight of  $250 \pm 1$  mg were prepared by blending theophylline with HPMC E50LV, E4M or E10M in the ratio of 4:1 for 10 min at 100 rpm in a Turbula<sup>®</sup> mixer (Type T2 C, Switzerland). The tablets were compressed using a single punch-tableting machine (Model MTCM-1, Globe Pharma, US) at 1500 psi (5.55 kN). The die wall was lubricated each time after tablet compression with a 1 % w/v suspension of magnesium stearate (Acrös Organics, New Jersey, USA) in acetone (Fisher Scientific, UK). The breaking force for five tablets was determined using Schleuniger 8M tester (Switzerland).

## 2.7. Dissolution test

### 2.7.1. *Effect of pH and agitation*

Drug release profile of the formulations was investigated in six different dissolution media to evaluate the degree of sensitivity of the different methoxyl substitution grades of HPMC to pH. A series of buffer solutions that simulated the stomach and intestinal conditions in fasted and fed states with the pH values of 1.2, 2.2, 5.8, 6.8, 7.2 and 7.5 were used. The dissolution testing was conducted for 310 min for all formulations. The influence of agitation on drug release was studied and detailed in a previous study [38]. All theophylline-HPMC (E50LV, E4M and E10M) formulations were tested using this developed methodology and it facilitated the discrimination of the effect of agitation on the formulations where different viscosity or molecular weight grades of the HPMC were used.

### 2.7.2. *Influence of ionic strength*

Sodium chloride was used to regulate the ionic strengths of the media from 0 to 0.4 M in buffers with pH values of 1.2, 2.2, 5.8, 6.8, 7.2 and 7.5. The ionic strength of the fluids of the GI tract in man under both fasted and fed states and various physiological pH conditions cover a range of 0 - 0.4 M [39]. Sodium chloride is the mid-range of the lyotropic series and has the ability to salt out polymers, hence is often used as the agent for ionic regulation of dissolution media [39, 40]. Both theophylline E50LV, E4M and E10M formulations were tested by varying ionic strength of the dissolution media as reported by Asare-Addo et al. [41]. The absorbance of the released theophylline was measured at 271 nm using a UV/Visible spectrophotometer (Varian, Cary 50).

## 2.8. Similarity factor

Similarity factor was calculated as detailed in Asare-Addo et al. [38, 42] for the effect of agitation. Drug release in water was used in the determination of  $f_2$  values where ionic strength was concerned as detailed in Asare-Addo *et al.*, [41]  $f_2$  values above 50 is an indication of similarity, while less than 50 indicates dissimilarity between two dissolution profiles [43].

## 2.9. Dissolution parameters

The mean dissolution time (MDT), which is the mean time for the drug to dissolve under *in-vitro* dissolution conditions, is a model-independent method and is suitable for dosage forms that exhibit different mechanisms of drug release [39, 44]. As this study uses different viscosities of HPMC polymers, it provides a way of comparing the dissolution profiles. The dissolution efficiency (DE) and mean dissolution rates (MDR) were also calculated. The equations for the calculation of these dissolution parameters are detailed elsewhere [45].

## 2.10. Kinetics of drug release

The kinetics of drug release was analysed using Peppas equation [46] as detailed in a previous study [38]. In general for drug release from films [46],  $n$  values close to 0.5 are indicative of the drug release being primarily by diffusion. Values of  $n = 1$  gives an indication that drug is released by relaxation and erosion processes. Anomalous transport is the term given to  $n$  values between 0.5 and 1. This is an indicator of the superposition of both processes. However, for the tablet matrices which are cylindrical in shape, the  $n$  values are slightly different as derived by [46] Values of  $n$  of up to 0.45 suggest Fickian diffusion, and values above 0.89 suggest Case-II transport. Values between these two suggest the occurrence of anomalous transport.

## 2.11. Differential Scanning Calorimetry (DSC)

### *Part A:*

Samples of physical mixtures of drug and polymer after the mixing process in section 2.6 were placed in standard 40  $\mu$ L aluminium crucibles and sealed. The aluminum pans were heated (from 25 °C to 300 °C at 10 °C/min under nitrogen gas) to examine potential drug interactions.

*Part B:*

Flat-faced 4 mm disks with target weights of 20 mg each were produced from all four theophylline-HPMC (E50LV, E4M and E10M) mixtures and compressed using a single punch tableting machine (Model MTCM-1, Globe Pharma, US) at 1500 psi (5.55 kN). The die wall was lubricated each time after tablet compression with a 1 % w/v suspension of magnesium stearate in acetone. The discs were hydrated for 5, 10, 15 and 20 min using purified water, pH 1.2, pH 1.2 (0.2 M ionic strength) and pH 1.2 (0.4 M ionic strength), placed in standard aluminium pans and sealed with a lid. The aluminium pans were firstly cooled from ambient temperatures (~25 °C) to -30 °C at 55 °C/min, to freeze any unbound (free) water; maintained at -30 °C for 5 minutes for equilibration and then heated from -30 °C to 50 °C at 10 °C/min under nitrogen gas to determine amount of free and bound water and hydration rate of the tablets using endothermic scanning of the melted free water [41, 47]. These experiments were carried out in triplicate.

### 3. Results and discussion

#### *3.1. HPMC polymer and formulation characterization*

Triboelectrification experiments were performed to evaluate charging and adhesion behaviour of theophylline on addition of different HPMC polymers. The charge test for theophylline on its own indicated that the saturated charge is -23nC/g after shaking for two minutes (Table 1). The level of charge is relatively low compared to common API charge as reported previously [48]. Triboelectrification of polymers shows E4M to be charged positively against the stainless steel container, whilst E10M and E50LV both had slight electronegative charges. The magnitude of charge of E4M was notably higher than E10M and E50LV. In general, it was shown that the negative charge of theophylline decreased after blending with HPMC polymers. Theophylline charged negatively as did the blends, but the magnitude was reduced due to the presence of HPMC polymer in the blends. The charge generated by a material depends entirely on contact between surfaces. Generally, particulates that are fine tend to charge negatively. Larger particles on the other hand tend to charge positively. A hypothetical mechanism for particle size dependent charging was provided by Lacks and Levandovsky, [49]. It has been argued that collisions allow electrons trapped in high-energy states on one particle to transfer to the vacant low-energy states on another particle assuming that the surface density of trapped electrons is initially the same on all

particles [50, 51]. Therefore, as HPMC polymer is blended with theophylline, the charge that is measured is mainly that of the polymer despite the drug being in excess (by weight). All powder blends had similar adhesion to the walls of the vessel, irrespective of the chemistry or molecular weight of the polymer ( $p > 0.05$ ).

E chemistry polymers demonstrated different physical properties as summarized in Table 1. The mean diameter ranged between  $72.7 \pm 0.2$  and  $81.9 \pm 0.3$   $\mu\text{m}$ , which was further qualitatively confirmed by SEM images (Supplementary figure 1). E4M had the largest particle size with the narrowest size distribution (as indicated by the smallest span), the highest specific surface area and the roughest surface texture. On the other hand, E50LV showed the smallest size with widest size distribution, the smallest specific surface area and the smoothest surface texture among polymers tested (Table 1). The E chemistry polymers also had a water content range between 3.4 and 3.7 %w/w. The E chemistry 4:1 drug:HPMC formulations showed that they are robust formulations in terms of tablet hardness (50-76 kN). The rank order breaking force or mechanical strength of the E chemistry HPMC tablet matrices was  $\text{E10M} > \text{E50LV} > \text{E4M}$ .

### 3.2. Effect of agitation

Figure 1a shows the influence of agitation rate and sequence on drug release from tablets that contain the E chemistry HPMC grades. For matrices containing the low viscosity polymer E50LV, once in water with the applied agitation, fragments of the tablet were detaching from the matrix surface into the solution before a full gelatinous layer was formed, although none of the tablets actually disintegrated. Drug release increased with an increase in the agitation rate. Drug release rate was in the order of  $\text{E50LV} > \text{E4M} > \text{E10M}$  (For E4M and E10M, refer to Supplementary figure 2). This showed that the erosion occurring because of the increased agitation rate was more rapid for the HPMC with the lower molecular weight, which in this case was the E50LV. This could be explained as follows; The gel being formed on the surface of the tablet upon its introduction into media could limit the amount of drug being transported into the solution as drug moved from one medium condition to another and the change in the tablets geometry as a result of agitation meaning a decreased surface area for the next medium. The E10M tablet matrices however as compared to the E4M and E50LV tablet matrices was less prone to the effects of agitation due to its high elasticity  $G'$  hence, higher stress required to yield (Figure 5) [38].

A comparison of the two different agitations rates in the ascending order of 5-30 dpm and descending order of 30-5 dpm confirmed the susceptibility of the E50LV tablet matrices to the effects of agitation. All drug was released in pH 2.2 medium after just 120 min in the descending form of agitation (30-5 dpm) (Figure 2a). In the case of E4M matrices, the entire drug was released in pH 7.2 medium after 280 min with a starting agitation of 30 dpm, with 75 % of the drug released in pH 1.2 alone. When agitation was started at 5 dpm, 76 % of the drug was released after 310 min in pH 7.5 (Supplementary figure 3). The E10M showed resilience after the dissolution process of 310 min with a drug release of 77 % in the ascending order of agitation (5-30 dpm) and 89 % in the descending order (30-5 dpm) in pH 7.5 (Figure 2b). These results show that drug release can vary at different pHs for non-ionic polymers depending on the agitation rate and molecular weight of polymers. For example, for formulations that are not robust, the agitation could cause a relatively fast drug release resulting in a possible toxicity or making a drug unavailable at the targeted site [32, 52]. The generally fast rate of drug release from the tablet matrices rendered most of the dissolution profiles dissimilar or impossible to calculate (Table 2). Anomalous transport was the only mechanism of drug release from the E50LV tablet matrices (Table 2). The E4M and E10M tablet matrices on the other hand were dominated by Fickian diffusion with anomalous transport occurring over the increasing order of agitation (5-30 dpm) with respective values of 0.50 and 0.47 (Table 2).

### 3.3. Effect of ionic strength

Figure 3 a and supplementary figures 4 a and b shows the impact of ionic strength on drug release from E50LV, E4M and E10M tablet matrices respectively with supplementary figure 5 showing the drug release rates. The ionic strength of buffers used to control pH varied from 0.05-0.14 M. The addition of 0.2 M and 0.4 M sodium chloride means the actual ionic concentration strength at the 0.2 M level ranged between 0.25-0.34 M and for the 0.4 M ranged between 0.45-0.54 M but for consistency, the ionic strength of the added NaCl is used in legends.

Similarity calculations were not valid for release of theophylline from the E50LV (Table 3). This was a result of the quick drug release from its matrices thereby not having enough time points for a valid analysis. With regards to the E4M tablet matrices, similarity was only obtained in the pH media with an  $f_2$  value of 95. The E10M tablet matrix was the most robust of the formulations. Despite the fall in the  $f_2$  parameter as ionic strength increased, release

profiles were similar at different ionic strengths with  $f_2$  values of 63 and 50 in pH-controlled media of ionic strengths 0.2 and 0.4 M respectively (Table 3). At pH 1.2 only, drug release from E50LV tablet matrices increased after 1 hour from  $64.76 \pm 0.79$  % in deionised water to  $76.14 \pm 1.86$  % when ionic strength was increased to 0.4 M.  $66.51 \pm 2.66$  % and  $65.87 \pm 2.24$  % of drug had been released from the tablet matrices for the E4M formulation in deionised water or pH1.2 medium without added salt (Figure 3b). Upon 0.2 and 0.4 M NaCl, drug release from tablet matrices increased to  $83.65 \pm 7.48$  % and  $83.08 \pm 5.02$  % respectively. This significant increase was not reproduced for drug release from the E10M tablet.  $50.72 \pm 5.58$  % of drug was released in deionised water, increasing to  $56.42 \pm 4.01$  % on addition of 0.2 M NaCl and a further increase occurred with 0.4 M NaCl (Figure 3b). At the low ionic strengths (buffers with no added salt), the polymer hydration seems to be unaffected. Higher ionic strengths however may have led to a loss of gel integrity of the E50LV and E4M matrices hence the increase and difference in their drug release profiles. The E10M was thus more resilient to the influence of ionic strength in comparison to the E50LV and E4M formulations due to its increased viscosity. The results show that despite HPMC being a non-ionic polymer, the medium ionic composition can influence its behaviour drug release behaviour. This was in agreement with work done by Kavanagh and Corrigan [53]. They showed that an increase in ionic strength brought about a decrease in matrix erosion rate with the phenomenon being prevalent in low molecular weight HPMC grades. Alderman [54] also noted that as the ionic strength of the medium increases, the polymer molecular chains loose water of hydration due to ions competing for the available water.

MDTs generally decreased with increasing ionic strength for all matrices. The E50LV tablet matrix exhibited anomalous transport in deionised water and buffers, with Fickian kinetics becoming more dominant with increasing ionic strength (Table 3). Fickian release dominated for all E4M and E10M formulations.

### *3.4 Evaluation of gel strength of HPMC polymer*

It has been observed that the different HPMC grades show different drug release behaviour. In order to clarify these findings, the rheological properties of the polymers used were determined by oscillatory rheometry. The stiffness and degree of inter-particle interaction were evaluated by stress sweep rheological measurements. Figure 4a shows the yield stress and gel strength for different HPMC grades. The yield stress can be inferred from the stress at which  $G'$  starts to decrease. The stress required to yield or to erode were 1 Pa, 150 Pa, and

320 Pa, for the E50 LV, E4M and E10M respectively. This result indicates a high degree of inter-particle interactions which suggests a lower degree of erosion for E10M [55, 56]. The stiffness of the gel was also found to be varied from 2.5 Pa, 176.2 Pa and 408.3 Pa for the E50LV, E4M and E10M respectively. The lower  $G'$  value can be explained by a softer gel being formed after tablet introduction into the dissolution media. The reduction in stiffness of the gel indicates faster drug release [57]. Figure 4b and supplementary figure 6a and b shows elastic modulus  $G'$  and viscous modulus  $G''$  versus frequency sweep oscillation for E50LV, E4M and E10M. E50LV, E4M and E10M exhibit similar classical temporary network response with  $G''$  Greater than  $G'$  at low frequencies, indicating that the polymer behaves as a viscous liquid. By increasing the frequency  $G'$  increased and  $G''$  decreased gradually until they crossed over at the critical gel point frequency (indicated by black arrow). At higher frequencies,  $G'$  becomes greater than  $G''$  indicating that the polymer behaves as a more elastic material [58]. The observed difference in both moduli for different HPMC grade is normal since polymers with higher molecular weight increase the entanglement density [59]. E10M had the strongest  $G'$  and  $G''$  with 1.4 Pa frequency to get to gel critical point indicating that E10M is more elastic [58, 59]. There is a poor evidence of gel formation in figure 4b. Therefore E50LV system is more susceptible to erosion and/or dilution during drug release study [59]. Talukdar et al. reported no detectable influence of the ionic strength of the medium on the rheological properties of HPMC [59]. This is in good agreement with the present study, as shown in figure 5a and b. There was no significant difference ( $P > 0.05$ ) in yield stress figure 5a and  $G'$  figure 5b of the same HPMC grade samples treated with the two different ionic strength solutions (pH 1.2 media (no NaCl) and pH 1.2 media (0.4M NaCl)), this may be due to non-ionic charge of HPMC polymer. This result thus explained the independence of drug release in different ionic strength media.

### 3.4. DSC analysis

DSC traces showed no material interaction between the drug, theophylline, and the HPMC polymers (Figure not included). DSC hydration showed the E50LV tablet matrices to generally have more bound water compared to the E4M and E10M tablet matrices (Supplementary figure 7) suggesting that it would be more prone to food effects and that the penetration of the various media into the matrix used happened more quickly [41]. All polymers showed an increase in bound water with the increase in ionic strength thus agreeing



with findings for bound and free water states in K chemistry HPMC matrices [41]. As the ratio of bound water to free water increases, the amount of water available for polymer hydration is reduced thereby the gel layer for controlling drug release is somewhat compromised. Yoshioka et al. [27] and Aoki et al. [26] showed that bound water did not contribute significantly to drug release and that water uptake by hydrophilic matrices was dependant on the amount of free water present in the system. The amount of drug released at the 10 min time point also correlated with the DSC hydration experiments as in [41]. The theophylline release increased with an increase in the ionic concentration strength. In the highest ionic concentration strength medium, the amount of bound water was similar for all the formulations tested suggesting that the strength of the gel played an important role also in the drug release pattern as also in [41].

#### 4. Conclusion

HPMC E50LV particles were of a smaller size, smaller surface area and smoother surfaces than E4M and E10M grades of HPMC. The polymers E4M, E10M and E50LV are effective in dissipating electrostatic charge of the API. Drug release from E50LV and E4M matrices was affected by changing agitation and ionic strength. With regards to agitation, there was an increase in drug release with an increase in agitation. Ascending and descending rates of agitation were used to differentiate between all three formulations and showed the E10M tablet matrices to be more resilient to the impact of agitation. Incremental increases in ionic strength also had a profound effect on the E50LV and E4M tablet matrices. This could be attributed to the fact that an increase in the ion concentration in a polymer solution decreases the solubility or hydration of the polymer thereby reducing the amount of available water for hydrating the polymer. Rheological evaluation of the gels indicated a high degree of interparticulate interactions which can suggest a lower degree of erosion for E10M as compared to the other polymers. The E10M polymer was also resilient to the influence of ionic strength. DSC studies on the hydration states also proved useful in explaining drug release from the E-chemistry HPMC polymers. This highlights the importance of choosing the right HPMC polymer for the extended release matrix.

#### 5. Acknowledgements

The authors are grateful to Colorcon for the free gift of hypromellose and to the University of Huddersfield for funding this research.



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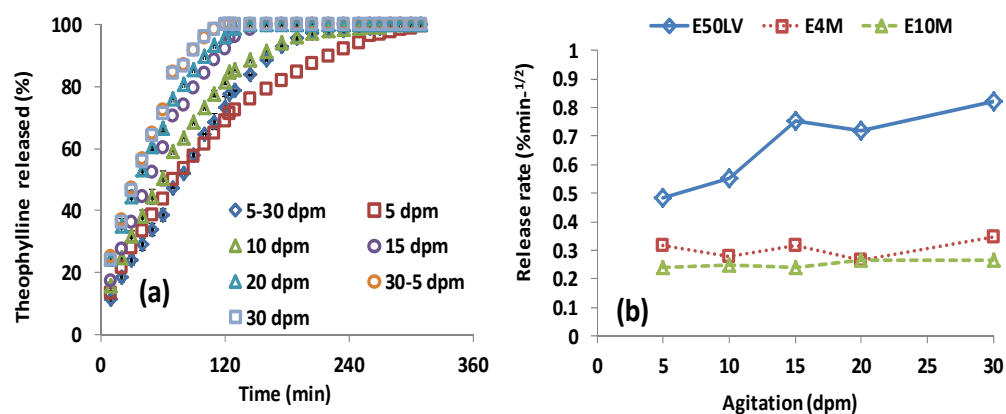
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## Figure captions

**Figure 1** - The effect of rate and order of agitation on drug release from HPMC (a) E50LV tablet matrix formulations (**SD, n=3**) (b) Drug release rates of the E chemistry tablet formulations with respect to the differing agitations. **Standard deviations were smaller than the symbol size and as such were not shown here.**

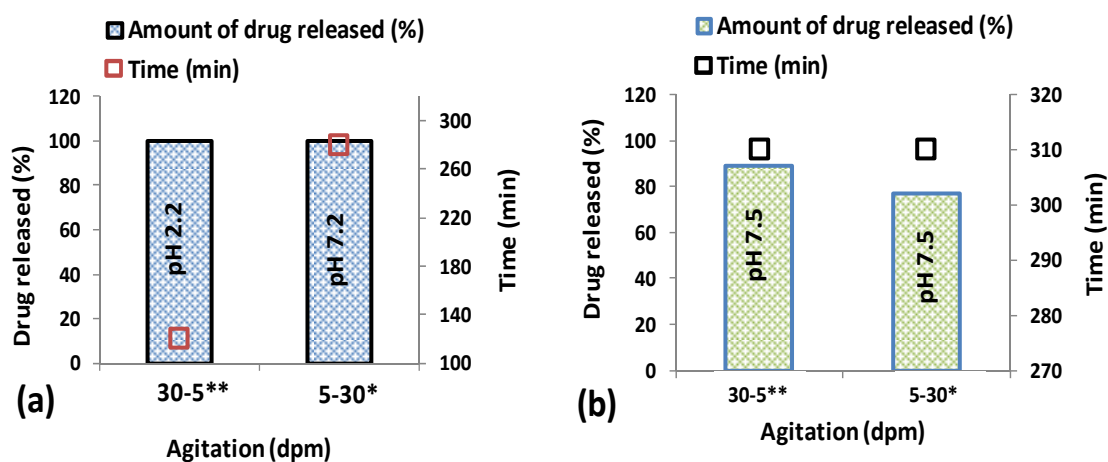


### Note:

Ascending order of agitation is depicted as 5 - 30 dpm and is when agitation was increased by 5 dpm every time the cylinder containing the drug moved from one vial to the other. Thus, in pH 1.2 agitation was 5 dpm, in pH 2.2 - 10 dpm, in pH 5.8 - 15 dpm, in pH 6.8 - 20 dpm, in pH 7.2 - 25 dpm and in pH 7.5 - 30 dpm.

Descending order of agitation is depicted as 30 - 5 dpm and is when agitation was decreased by 5 dpm every time the cylinder containing the drug moved from one vial to the other. Thus, in pH 1.2 agitation was 30 dpm, in pH 2.2 - 25 dpm, in pH 5.8 - 20 dpm, in pH 6.8 - 15 dpm, in pH 7.2 - 10 dpm and in pH 7.5 - 5 dpm [20]

**Figure 2** - The amount of drug released (%) from HPMC (a) E50LV (b) E10M tablet matrix formulations when increasing the agitation rate during the dissolution test (SD, n=3).



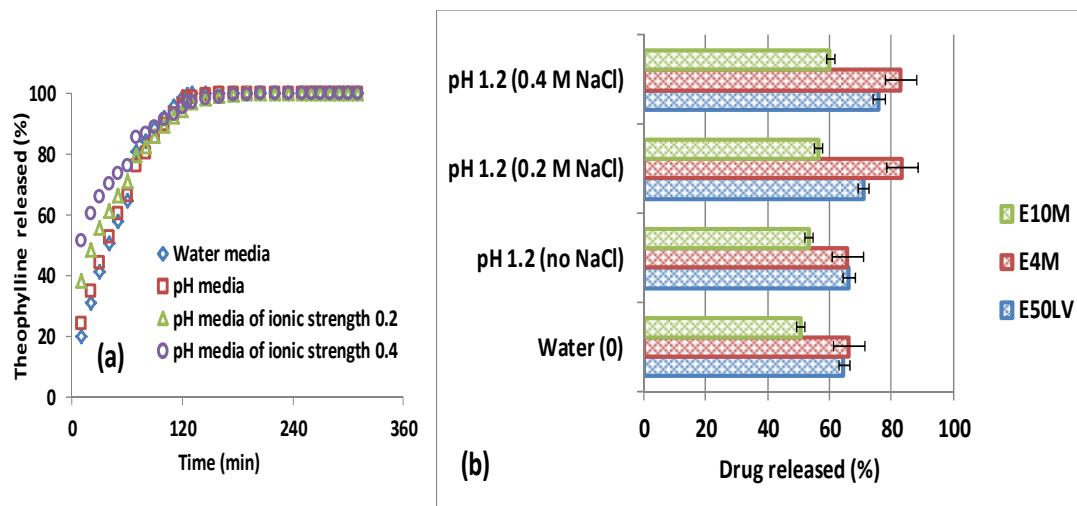
Note:

\*Ascending order of agitation; agitation was increased by 5 dpm every time the cylinder containing the drug moved from one vial to the other. Thus, in pH 1.2 agitation was 5 dpm, in pH 2.2 - 10 dpm, in pH 5.8 - 15 dpm, in pH 6.8 - 20 dpm, in pH 7.2 - 25 dpm and in pH 7.5 - 30 dpm.

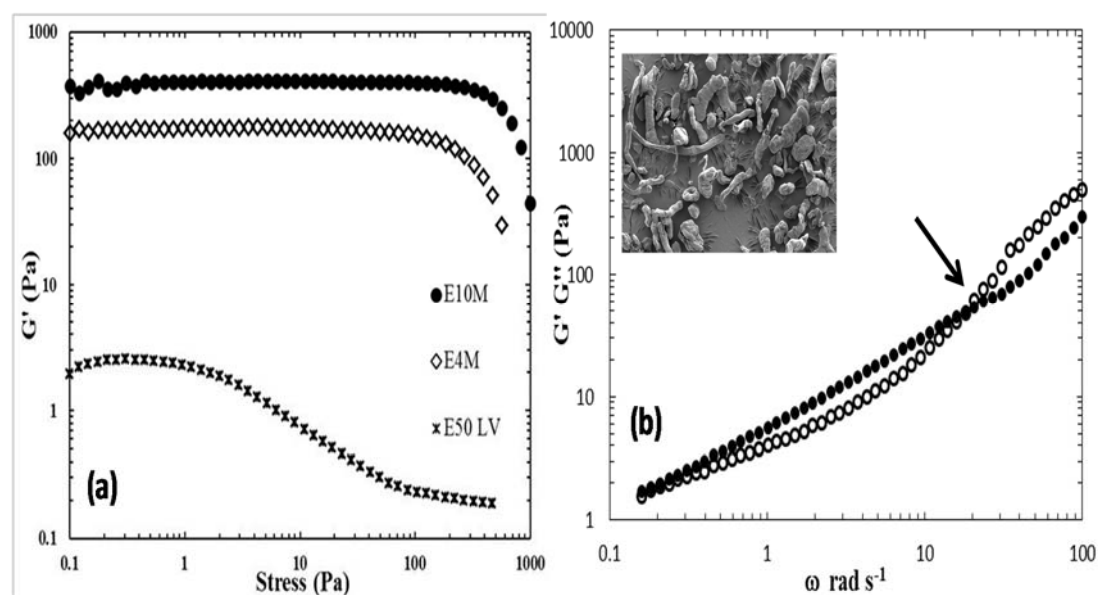
\*\*Descending order of agitation; agitation was decreased by 5 dpm every time the cylinder containing the drug moved from one vial to the other. Thus, in pH 1.2 agitation was 30 dpm, in pH 2.2 - 25 dpm, in pH 5.8 - 20 dpm, in pH 6.8 - 15 dpm, in pH 7.2 - 10 dpm and in pH 7.5 - 5 dpm [20].



**Figure 3** -The effect of ionic strength on drug release from HPMC (a) E50LV tablet matrix formulations (b) Amount of drug released from E chemistry HPMC tablet matrices formulations after 1 hour in media of varying ionic strengths (**SD, n=3**)



**Figure 4** - Stress sweep for at 1.5 HZ for 5% HPMC as a function of different HPMC grade, E10M, E4M and E50LV (a) Elastic ( $G'$  unfilled symbols) and viscous ( $G''$  filled symbols) moduli as a function of frequency for E50LV (circle symbols) (b)



**Figure 5** - Yield stress measurement at 37 °C for E50LV, E4M and E10M, dispersed in different ionic strength medium (a) Elastic modulus measurement at 37 °C for E50LV, E4M and E10M dispersed in different ionic strength medium (b) (SD, n=3).

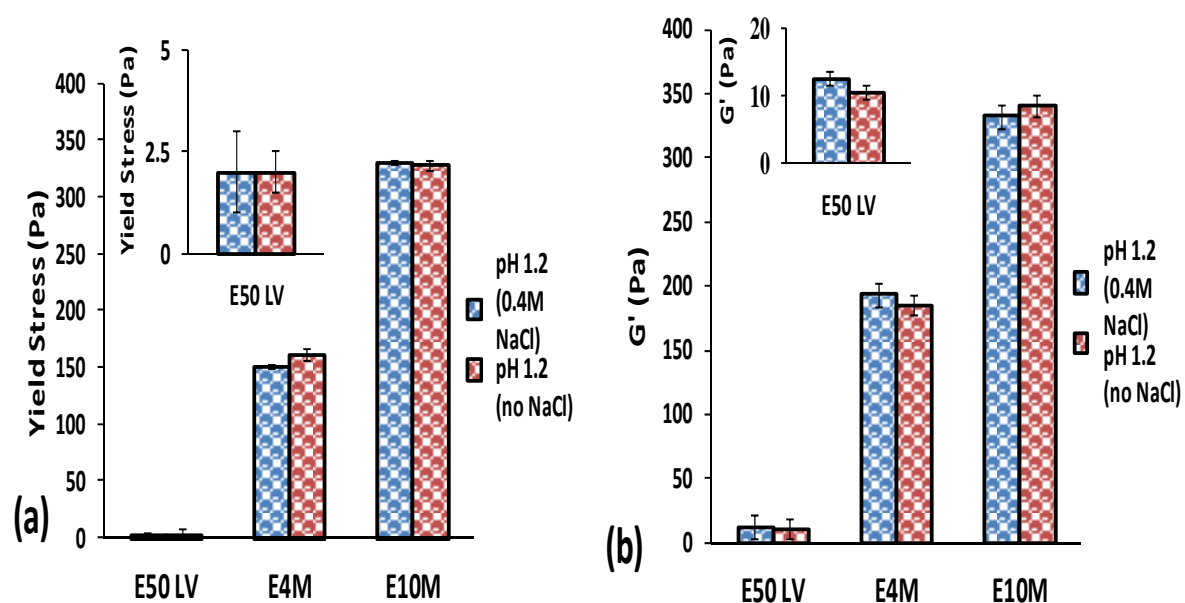


Table 1: Tribo-electric properties of HPMC polymers, theophylline and their powder blends and Volume mean diameter (VMD), span, BET surface area, roughness, true density and water content, for E4M, E10M and E50LV HPMC polymers (**SD, n=3**)

Powders and Blends	Charge	Adhesion	VMD	Span	BET surface	Roughness	True	Water
	Q <sub>sat</sub> (nC/g)	*A <sub>dh</sub> (%)			area (m <sup>2</sup> /g)		density (g/cm <sup>3</sup> )	content (%)
	-23.1 ±	15.0 ±						
<b>Theophylline</b>	0.8	2.3	-	-	-	-	-	-
	26.9 ±	17.9 ±	81.9 ±	1.4 ±				
<b>E4M</b>	5.38	2.0	0.3	0.0	0.26 ± 0.02	1.30 ± 0.11	1.35 ± 0.01	3.7
		12.1 ±	77.3 ±	1.6 ±				
<b>E10M</b>	-5.2 ± 1.0	0.6	0.5	0.0	0.24 ± 0.02	1.12 ± 0.07	1.37 ± 0.01	3.4
			72.7 ±	1.7 ±				
<b>E50LV</b>	-1.5 ± 0.4	9.9 ± 1.3	0.2	0.0	0.14 ± 0.02	0.72 ± 0.13	1.36 ± 0.01	3.7
		15.9 ±						
<b>E4M Blend</b>	-4.0 ± 0.2	0.2	-	-	-	-	-	-
		16.4 ±						
<b>E10M Blend</b>	-5.0 ± 0.7	1.3	-	-	-	-	-	-
<b>E50LV</b>		16.6 ±						
<b>Blend</b>	-5.1 ± 0.2	0.6	-	-	-	-	-	-

\*A<sub>dh</sub> is the powder particles adhered to the walls of the shaking container.

Table 2: Effect of agitation rate on similarity factor ( $f_2$ ) and mechanism of drug release for formulated tablets

Tablet Formulation	Agitation	RSQ	n	$f_2$
E50LV	5	0.9856	0.5816	51
E50LV	10	0.9742	0.5892	n/a
E50LV	15	0.9894	0.6659	-
E50LV	20	0.9909	0.557	-
E50LV	30	0.9883	0.6036	-
E50LV	5-30	0.9937	0.7484	52
E50LV	30-5	0.9877	0.5855	-
E4M	5	0.9873	0.4001	44
E4M	10	0.9913	0.2779	n/a
E4M	15	0.9803	0.2353	-
E4M	20	0.9888	0.2387	55
E4M	30	0.9835	0.2148	-
E4M	5-30	0.9977	0.503	31
E4M	30-5	0.9834	0.2027	-
E10M	5	0.9929	0.3794	54
E10M	10	0.9939	0.324	n/a
E10M	15	0.9945	0.2601	50
E10M	20	0.9922	0.2854	48
E10M	30	0.9922	0.2507	36
E10M	5-30	0.9971	0.465	60
E10M	30-5	0.9764	0.2235	34

Note: n/a as release profile at 10 dpm used as reference

Table 3: Similarity factor ( $f_2$ ) and release parameters for tablet matrices

Tablet Formulation	Ionic strengths	Agitation (dpm)	Drug-release characteristics					$f_2$
			DE <sub>310min</sub> (%)	MDT (min)	MDR (%min <sup>-1</sup> )	RSQ (r <sup>2</sup> )	n	
E50LV	Water (0)	20	85.72	39.43	0.28	0.9886	0.6733	n/a
	(no salt)	20	85.62	36.48	0.26	0.9909	0.5570	-
	(+0.2 M salt)	20	87.46	29.04	0.20	0.9941	0.3705	-
	(+0.4 M salt)	20	89.79	23.06	0.16	0.9900	0.2515	-
E4M	Water (0)	20	81.58	21.18	0.14	0.9935	0.2686	n/a
	(no salt)	20	79.40	21.44	0.14	0.9888	0.2387	95
	(+0.2 M salt)	20	91.59	16.97	0.11	0.9577	0.1388	-
	(+0.4 M salt)	20	91.44	15.09	0.09	0.9786	0.1245	-
E10M	Water (0)	20	65.59	23.05	0.13	0.9927	0.3121	n/a
	(no salt)	20	66.55	22.65	0.13	0.9922	0.2854	82
	(+0.2 M salt)	20	68.36	20.16	0.11	0.9949	0.2387	63
	(+0.4 M salt)	20	77.35	16.84	0.11	0.9848	0.2677	50

Note: n/a as release profile at 20 dpm in water was used as reference